Allergen immunotherapy in the European regulatory environment

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Abstract
Allergen immunotherapy (AIT) modulates the immune system to prevent and relieve allergic symptoms. Unlike allergen avoidance and medication to control symptoms, AIT targets the underlying pathophysiology of allergic diseases. AIT is now considered a type of therapeutic vaccination. This article focuses on the current regulatory environment in the EU and the special considerations in designing clinical trials evaluating AIT products.

Background
Allergen immunotherapy (AIT) modulates the immune system to prevent and relieve allergic symptoms.[1] Unlike allergen avoidance and medication (e.g. antihistamines and corticosteroids) to control symptoms, AIT targets the underlying pathophysiology of allergic diseases. AIT is now considered a type of therapeutic vaccination because it uses antigens to treat an existing illness by modulating the immune system.

In AIT, allergen is administered subcutaneously or sublingually at regular intervals to modulate the immune response. The aim is to reduce associated symptoms, decrease the need for medication, and prevent the development of new allergies and asthma.[2] Traditionally, AIT products contain allergens isolated from biological sources such as pollen or house dust mites. These can be used unmodified or denatured with aldehydes and may be mixed with an adjuvant.

AIT is indicated in patients whose allergies interfere with daily activities or sleep despite allergen avoidance and medication, who have moderate-to-severe allergic symptoms when exposed to aeroallergen, and who are sensitised to allergen-specific immunoglobulin E.[3] These patients also often have co-existing asthma.

Allergen products for subcutaneous AIT are mainly applied as depot formulations, meaning that the drug is injected as a localised mass. AIT is administered in escalating doses every 7 and 14 days for depot solutions and every 3 to 7 days for aqueous solutions (Figure 1). When the maximum tolerated dose is reached, the injection intervals can be extended to every 4 to 8 weeks. For airway allergies (allergy-induced asthma), the overall duration of subcutaneous AIT should be at least 3 years.[3]

Regulation of allergen products in the EU
Previously, AIT products were marketed mainly based on expert opinion, and regulatory oversight was limited. However, in the last 20 years, clinical data is increasingly needed to access the market.[4]

In the EU, according to the Directive 2001/83/EC, adopted in 2004, therapeutic allergen products are considered medicinal products, substances, or combination of substances for diagnosing, treating, or preventing a disease.[5] Generally, these products require marketing authorisation to be commercialised.

EU Directive 2001/83/EC greatly advanced the legal framework for allergen products, although market access in EU member states continues to be heterogeneous. According to article 5 of EU Directive 2001/83/EC, allergen products, especially products prepared for specific patients (named patient products (NPPs)), can be prescribed to individuals in EU member states without marketing authorisation.

Many EU member states have passed specific laws adopting EU Directive 2001/83/EC.[4] An example is the *Therapieallergene-Verordnung* (Therapy Allergens Ordinance) in Germany (see Box opposite).

Clinical development of AIT products in the EU
In the EU, since 1993, with the exception of bee and wasp venom preparations, marketing

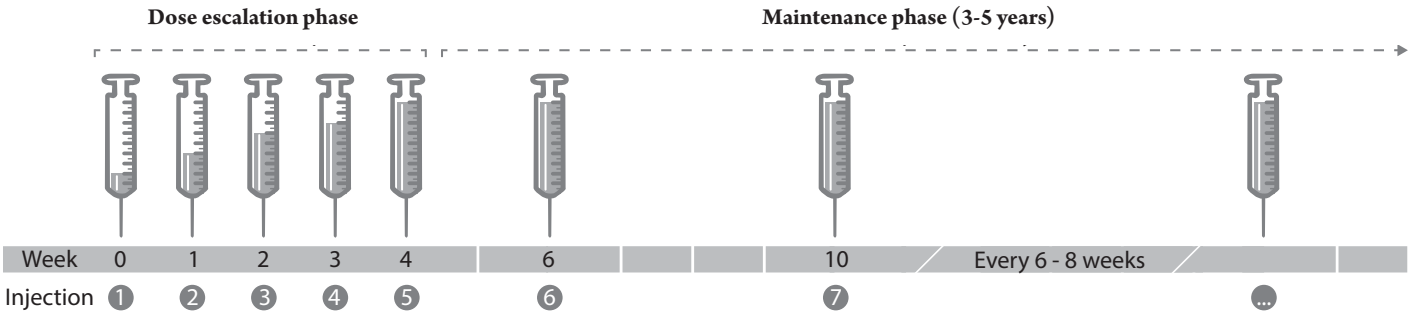

Figure 1. Example of a dosing schedule of subcutaneous AIT
During the dose-escalation phase, increasing doses of the allergen are applied every 7 days for until the maximum tolerated dose is reached. During the maintenance phase, the time between injections can be extended to every 4 to 8 weeks.

authorisation has only been granted if at least one double-blind placebo-controlled trial has been successfully completed. More stringent requirements for AIT clinical trials have resulted in a significant improvement in the quality of the data.[3]

Since 2004, EU member states have had to follow Good Clinical Practice guidelines as established by the Clinical Trials Directive (EU Directive 2001/20/EC). As a result, many randomised double-blind placebo-controlled trials assessing AIT products have been conducted in recent years. However, because of the seasonal nature of many allergic diseases and the lasting immunological changes induced by AIT, these clinical trials can be very time-consuming and costly, especially if a disease-modifying effect is the intended claim.[4]

In addition, since 2008, AIT clinical trials must be designed according to the Guideline on the Clinical Development of Products for Specific Immunotherapy for the Treatment of Allergic Diseases (CHMP/EWP/18504/2006).[4,7] This guideline addresses efficacy and safety measures for AIT products based on active substances (e.g. allergen extracts, recombinant allergens, purified native allergens, and modified

The Therapy Allergens Ordinance in Germany

In 2005, Germany introduced an exemption for NPPs for therapeutic purposes. AIT products manufactured for an individual patient were marketed as NPPs and did not require a marketing authorisation. This was independent of previously authorised products from the same allergenic source.[3]

Since 2008, the Therapy Allergens Ordinance has governed AIT products distributed as NPPs and used to treat the most frequent allergies.[3] Individual formulations containing any of the following allergen extracts require marketing authorisation:

- *Poaceae species* (grasses) excluding *Zea mays* (maize)
- *Betula species* (birch)
- *Alnus species* (alder)
- *Corylus species* (hazel)
- *Dermatophagoides species* (house dust mite)
- Bee venom
- Wasp venom

For NPPs that were marketed before the Therapy Allergens Ordinance came into effect, a transition procedure was created. These NPPs can still be distributed while the marketing authorisation application is being processed. This allows companies to conduct clinical trials and compile full marketing application dossiers to evaluate the efficacy and safety of these products.[2,3] All other allergen extracts, other than those listed above, produced as NPPs do not require marketing authorisation and are not officially monitored for quality, efficacy, and safety, or governmental batch release.

The application for marketing authorisation must include the results of all preclinical and clinical trials, as well as any results from additional testing. AIT products are only authorised for indications and patient groups for which safety and efficacy have been proved.[2]

allergens)[7] and is applicable to clinical trials on AIT regardless of the affected organ system, allergen source, allergen product, or route of administration.

Considerations for different kinds of AIT clinical studies in the EU according to CHMP/EWP/18504/2006

Phase I trials

AIT products should only be tested in patients with allergies because healthy individuals do not react to and are not put at risk by exposure to allergens.

Dose-finding studies

Dose-finding studies include multiple arms each with short-term treatment (e.g. 2 to 4 months) at a different dose. The primary efficacy measure can be a provocation test (e.g. conjunctival, nasal, or bronchial, or whole-body allergen exposure in an allergen challenge chamber) or other clinical endpoint assessing allergy severity.

Pharmacokinetic and pharmacodynamic studies

Pharmocokinetic and pharmacodynamic studies are not possible for AIT products. Due to the nature of AIT, plasma concentrations of the active substance are usually not measurable. Effects of AIT on the immune system are assessed by changes in allergen-specific IgG levels, T-cell responses, or cytokine production or by changes in the target organ specific response, for example using provocation tests.

Confirmatory trials

Confirmatory trials on AIT should be performed using a double-blind placebo-controlled design (Figure 2). Generally, statistical superiority compared to placebo or another comparator must be demonstrated. Because local allergic adverse events are frequent with AIT, to maintain blinding, a placebo preparation with histamine should be considered.

Confirmatory trials should enrol only patients with mild symptoms prior to randomisation. Confirmatory trials should include a prospective baseline period with a controlled collection of symptoms and allergen exposure to avoid the effects of variable allergen exposure, for example, during pollen seasons.

For seasonal allergies, for the baseline and evaluation periods, exposure to the relevant allergen must be documented and the minimum pollen count must be defined. For perennial allergies (e.g. to house dust mites), variations of indoor allergen levels must be minimised. For example, cleaning of the patient's home should be completed before the start of the clinical trial and before baseline symptoms are measured. Also, allergen exposure should be documented for each patient.

For allergic rhinoconjunctivitis, the efficacy of AIT can be evaluated in a single pollen season for seasonal allergies or after one or two control periods for perennial allergies. However, a persistent effect due to changes in the immune system can only be demonstrated in long-term trials. Thus, the possible claims of efficacy differ depending on the duration of the trial (Table 1).

In confirmatory trials on allergic rhinoconjunctivitis, the primary endpoint reflects both symptom severity and the intake of rescue medication. Several combined scores that include both severity and rescue medication use have been developed.

Symptom severity is often assessed using patient self-reported symptom scores recorded daily during a defined period. A single harmonised symptom score does not exist for allergic rhinoconjunctivitis, although most trials use a 4-point rating scale to score nasal itching, sneezing, rhinorrhoea, nasal obstruction, ocular itching, grittiness, redness, and ocular tearing (Table 2). Medication use should be scored according to those needed to relieve the magnitude and duration of symptoms (Table 3). Whatever the primary efficacy endpoint chosen, the endpoint and what constitutes a clinically relevant effect should be pre-specified and justified in the study protocol. Secondary endpoints for confirmatory trials can include the total symptom score, the total medication score, individual symptom scores, health-related quality of life (using validated questionnaires), symptom load scored using a visual analogue scale, and symptom-free days.

Safety

MedDRA is used to code adverse events in AIT trials. Usually, adverse events are graded as mild, moderate, or severe and assessed for relatedness to trial medication. Serious adverse events, especially those related to the treatment, must be described in detail. Expected allergic side-effects are classified according to their timing (immediate or delayed) and the site of appearance

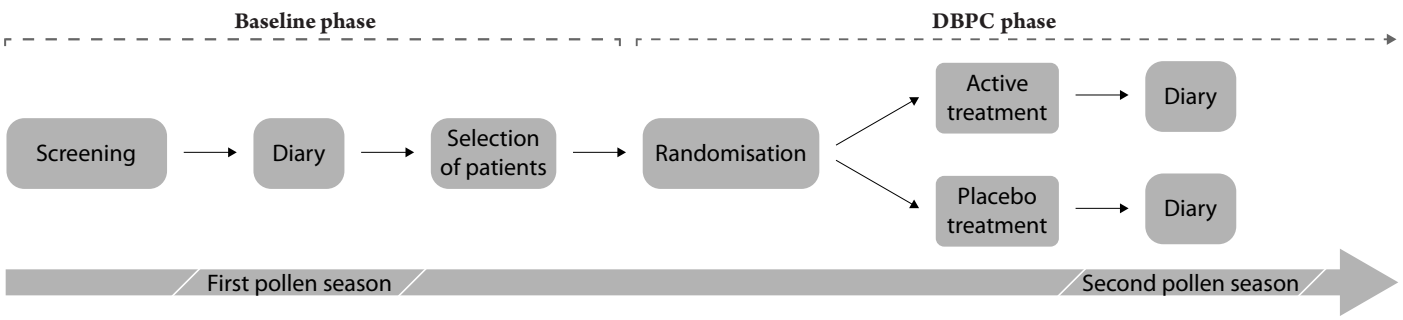

Figure 2. Example flow chart of a randomised double-blind placebo-controlled clinical trial with pollen AIT

During the baseline pollen season, symptoms and used medications of screened patients are assessed using a diary. Patients with a defined minimum level of allergic symptoms are selected for randomisation. Treatment with active therapy or placebo is performed before the following pollen season. Efficacy outcome measures (symptoms and medication use) are assessed during the pollen season using a diary.

Table 1. Claims for marketing authorisation[7]

Claim	Efficacy parameter
Treatment of allergic symptoms	Short-term clinical trials to show efficacy in the first pollen season after start of AIT or to show efficacy in perennial allergies after some months of treatment
Sustained clinical effect	Maintenance of significant and clinically relevant efficacy during 2 to 3 treatment years
Long-term efficacy and disease modifying effect	Sustained significant and clinically relevant efficacy in post-treatment years
Curing allergy	Sustained absence of allergic symptoms in post-treatment years

Table 2. Four-point rating scale for patient allergic symptoms

Score	Severity	Definition
0	Absent	No symptom evident
1	Mild	Clearly present
		Minimal awareness of symptom
		Easily tolerated
2	Moderate	Bothersome but tolerable
		Definite awareness of symptom
3	Severe	Poorly tolerated symptom
		Interferes with daily activities or sleeping

Severity is assessed on a scale from 0 to 3 for nasal (sneezing, running, blocked), conjunctival (itching, tear flow, redness) and bronchial symptoms (cough, wheezing, asthma with dyspnoea), giving a possible maximum daily score of 27.[7, 14]

Table 3. Example for scoring of medication

Type of medication	Unit	Score
Levocabastine nasal spray	1 puff	0.5
Levocabastine eye drops	1 drop	0.5
Loratadine or cetirizine tablets	10 mg	6
Oral corticosteroid	5 mg prednisolone or equivalent	4
Salbutamol	100 µg	1
Inhaled corticosteroids	400 µg budesonide or equivalent	6

The Medication Score rates the daily consumption of additional anti-allergic drugs according to the type, route and dose or number of applications. The combined Symptom Medication Score is calculated by the daily sum of the documented symptoms and the intake of additional anti-allergic medication.[14]

(local or systemic). Systemic reactions are graded using the European Academy of Allergy and Clinical Immunology or the World Allergy Organisation grading systems.[8,9] Other safety parameters collected in AIT trials include vital signs, routine blood and biochemical tests, and urinalyses.[8]

Challenges in clinical trials of AIT products

Patient selection

Because patients with allergic diseases are usually sensitised to more than one allergen group, selecting patients sensitised to a single allergen group is difficult. AIT trials should therefore include patients sensitised to a limited number of allergens, which must be identified and documented. Furthermore, to avoid biasing the outcome for one allergy, patients with concurrent allergies should be excluded, although not all co-sensitisations are clinically relevant. An example where a concurrent allergy may bias results are patients with allergic rhinoconjunctivitis caused by both a seasonal allergen (i.e. pollen) and a perennial allergy caused by animal dander from a pet. For patients with allergic airway disease, a baseline period is recommended before enrolment to ensure minimal symptoms at the start of treatment. Finally, patients should be excluded if they have received an AIT for the investigational allergen or a cross-reacting allergen in the previous 5 years or are receiving AIT for any allergen.

Unpredictable pollen seasons

Phase 3 AIT trials must be performed under natural allergen exposure, and the primary endpoint must include both symptom and medication scores.[2,10] These trials are also called "field trials".

The outcome of AIT clinical trials can be influenced by variations in pollen counts between different regions and across different years and the patient's individual pollen exposure during the pollen season, as well as interfering aero-allergens.[2,11,12] In addition, a patients' symptoms depend on their sensitivity to the investigated allergen, and they often depend more on the allergen content than on the total pollen load.[11]

Allergen challenge chambers have been used in dose-finding trials and may also be an option for confirmatory trials with allergens with unpredictable pollination and allergen content.

Allergen challenge chambers may be particularly useful in trials conducted over several years or during years with low pollen counts.[2,13] However, the results must be validated in studies assessing effects on allergies due to natural exposure, and the how measuring within or outside the pollen season must be evaluated.

Conclusion

Since European Directive 2001/83 EC was implemented in 2004, the regulatory environment for AIT products has changed. The requirements for demonstrating quality and efficacy have become stricter, creating new challenges. Despite these advances, market access for these products in the EU remains heterogeneous. Several European initiatives are now working on a harmonised approach to regulate these products.

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Conflicts of interest

The author is employed by Allergopharma GmbH & Co. KG.

References

1. Pfaar O, Bonini S, Cardona V, Demoly P, Jakob T, Jutel M et al. Perspectives in allergen immunotherapy: 2017 and beyond. Allergy. 2018 Jan;73 Suppl 104:5–23.
2. Roberts G, Pfaar O, Akdis CA, Ansotegui IJ, Durham SR, van Gerth Wijk R et al. EAACI Guidelines on Allergen Immunotherapy: Allergic rhinoconjunctivitis. Allergy. 2017 Sep 23. doi:10.1111/all.13317. [Epub ahead of print]
3. Pfaar O, Bachert C, Bufe A, Buhl R, Ebner C, Eng P et al. Guideline on allergen-specific immunotherapy in IgE-mediated allergic diseases: S2k Guideline of the German Society for Allergology and Clinical Immunology (DGAKI), the Society for Pediatric Allergy and Environmental Medicine (GPA), the Medical Association of German Allergologists (AeDA), the Austrian Society for Allergy and Immunology (ÖGAI), the Swiss Society for Allergy and Immunology (SGAI), the German Society of Dermatology (DDG), the German Society of Oto- Rhino-Laryngology, Head and Neck Surgery (DGHNO-KHC), the German Society of Pediatrics and Adolescent Medicine (DGKJ), the Society for Pediatric Pneumology (GPP), the German Respiratory Society (DGP), the German Association of ENT Surgeons (BV-HNO), the Professional Federation of Paediatricians and Youth Doctors (BVKJ), the Federal Association of Pulmonologists (BDP) and the German Dermatologists Association (BVDD). Allergo J Int. 2014;23(8):282–319.
4. Bonertz A, Roberts G, Hoefnagel M, Timon M, Slater J, Rabin R et al. Challenges in the implementation of EAACI Guidelines on Allergen Immunotherapy: A global perspective on the regulation of allergen products. Allergy. 2017 [cited 2017 Aug 11]. Allergy. 2018 Jan;73(1):64–76.
5. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the community code relating to medicinal products for human use Official Journal L - 311, 28/11/2004, p. 67-128; 2004.
6. 2001/20/EC D. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. In: Official Journal of the European Communities. 2001. Available at: https://www.eortc.be/services/doc/clinical-eu-directive-04-april-01.pdf.
7. Guideline on the clinical development of products for specific immunotherapy for the treatment of allergic diseases: European Medicines Agency (EMEA). Committee for Medicinal Products of Human Use (CHMP); 2008.
8. Passalacqua G, Baena-Cagnani CE, Bousquet J, Canonica GW, Casale TB, Cox L et al. Grading local side effects of sublingual immunotherapy for respiratory allergy: Speaking the same language. J Allergy Clin Immunol. 2013;132(1):93–8.
9. Cox L, Larenas-Linnemann D, Lockey RF, Passalacqua G. Speaking the same language: The World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System. J Allergy Clin Immunol. 2010;125(3):569–74, 574.e 1-574.e7.
10. Pfaar O, Demoly P, van Gerth Wijk R, Bonini S, Bousquet J, Canonica GW et al. Recommendations for the standardization of clinical outcomes used in allergen: immunotherapy trials for allergic rhinoconjunctivitis: An EAACI Position Paper. Allergy. 2014;69(7):854–67.
11. Rösner-Friese K, Kaul S, Vieths S, Pfaar O. Environmental exposure chambers in allergen immunotherapy trials: Current status and clinical validation needs. J Allergy Clin Immunol 2015;135(3): 636–43.
12. Durham SR, Nelson HS, Nolte H, Bernstein DI, Creticos PS, Li Z et al. Magnitude of efficacy measurements in grass allergy immunotherapy trials is highly dependent on pollen exposure. Allergy. 2014;69(5):617–23.
13. Pfaar O, Hohlfeld JM, Al-Kadah B, Hauswald B, Homey B, Hunzelmann N et al. Dose-response relationship of a new Timothy grass pollen allergoid in comparison to a 6-grass pollen allergoid. Clin Exp Allergy. 2017;47(11):1445–55.
14. Corrigan CJ, Kettner J, Doemer C, Cromwell O, Narkus A. Efficacy and safety of preseasonal-specific immunotherapy with an aluminium-adsorbed six-grass pollen allergoid. Allergy. 2005;60(6): 801–7.

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